MMPDCEDD

Microbial, Musculoskeletal
Proliferative Diseases
Dermatology & Diseases of the Developing World

Making Novel Antibacterials: New Targets or New Structures?

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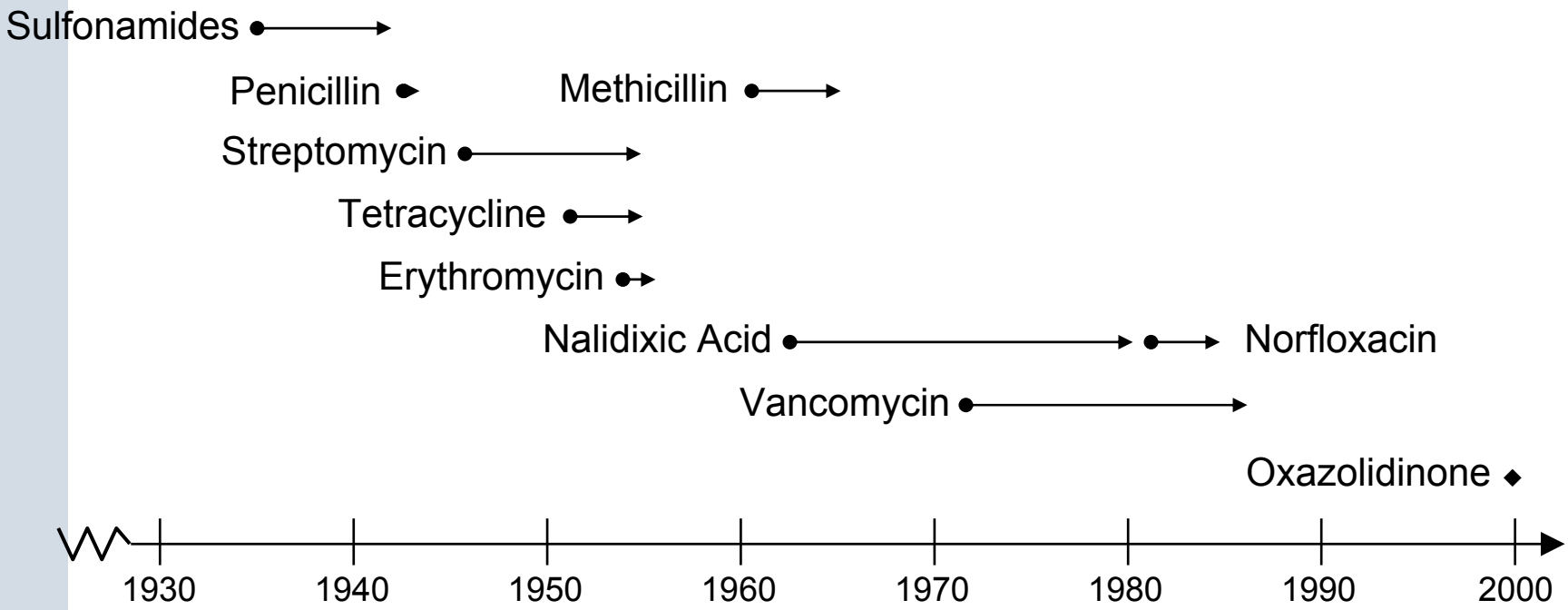
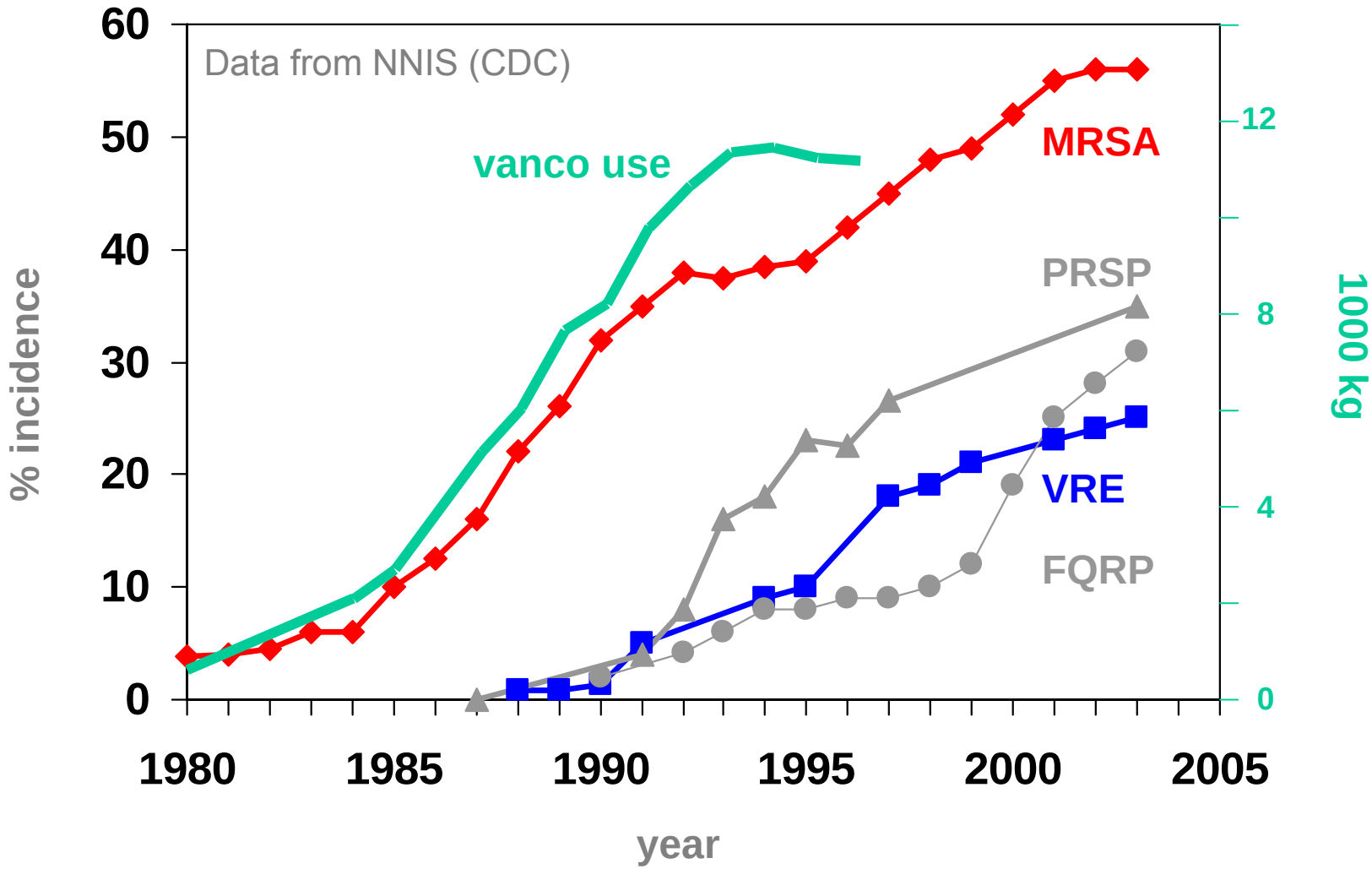
Clinical Resistance Develops Quickly



Resistant Strains Spread Rapidly



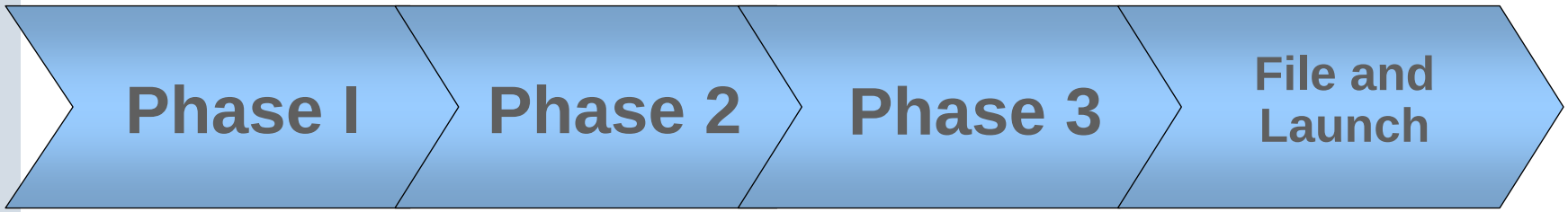
Top 10 Pharmaceutical Gaps (WHO)

1. **Infections from Resistant Bacteria**
2. Pandemic Influenza
3. Cardiovascular Disease
4. Diabetes
5. Cancer
6. Acute Stroke
7. HIV/AIDS
8. Tuberculosis
9. Neglected Diseases
10. Malaria

Dearth of *Novel* Antibacterials in Trials

EP-013420 *ketolide*
PTK-0796 *tetracycline*
PNU-288034 *oxazolidinone*
RBx7644 *oxazolidinone*
RWJ442831 *cephalosporin*
WCK771 *quinolone*
SB565154 *pleuromutilin*
SB742510 *pleuromutilin*

Cethromycin *ketolide*
BAL5788 *cephalosporin*
Garenoxacin *quinolone*
Sitafloxacin *quinolone*
Telavancin *glycopeptide*
Oritavancin *glycopeptide*
Faropenem *carbapenem*
Iclaprim *DHFR inhibitor*



CS-023 *carbapenem*
Tebipenem *carbapenem*

Dalbavancin *glycopeptide*
Doripenem *carbapenem*

Established Class
Novel Class

How to Find a Novel Agent?

- New molecular targets
  - found by comparative genomics
- Old molecular targets, but new structures
  - A Good Target Is Better than a New Target.
- Cell-based screening for novel structures

SB focused on the genomics approach.

Lack of Targets Is NOT the Problem !

Functional Area	# tested	# essential*
Cell wall & cell division	23	18
Glycolytic & amino acid pathways	33	18
Nucleotide metabolism	18	7
Lipid & CoA	22	17
Replication & nucleotide mod.	48	23
Protein secretion/modification	18	11
Translation/transcription	16	12
Unknown function	137	36
Two component signal trans.	13	6
Other	34	14
TOTALS	362	162

***In vivo* or *in vitro* essential**

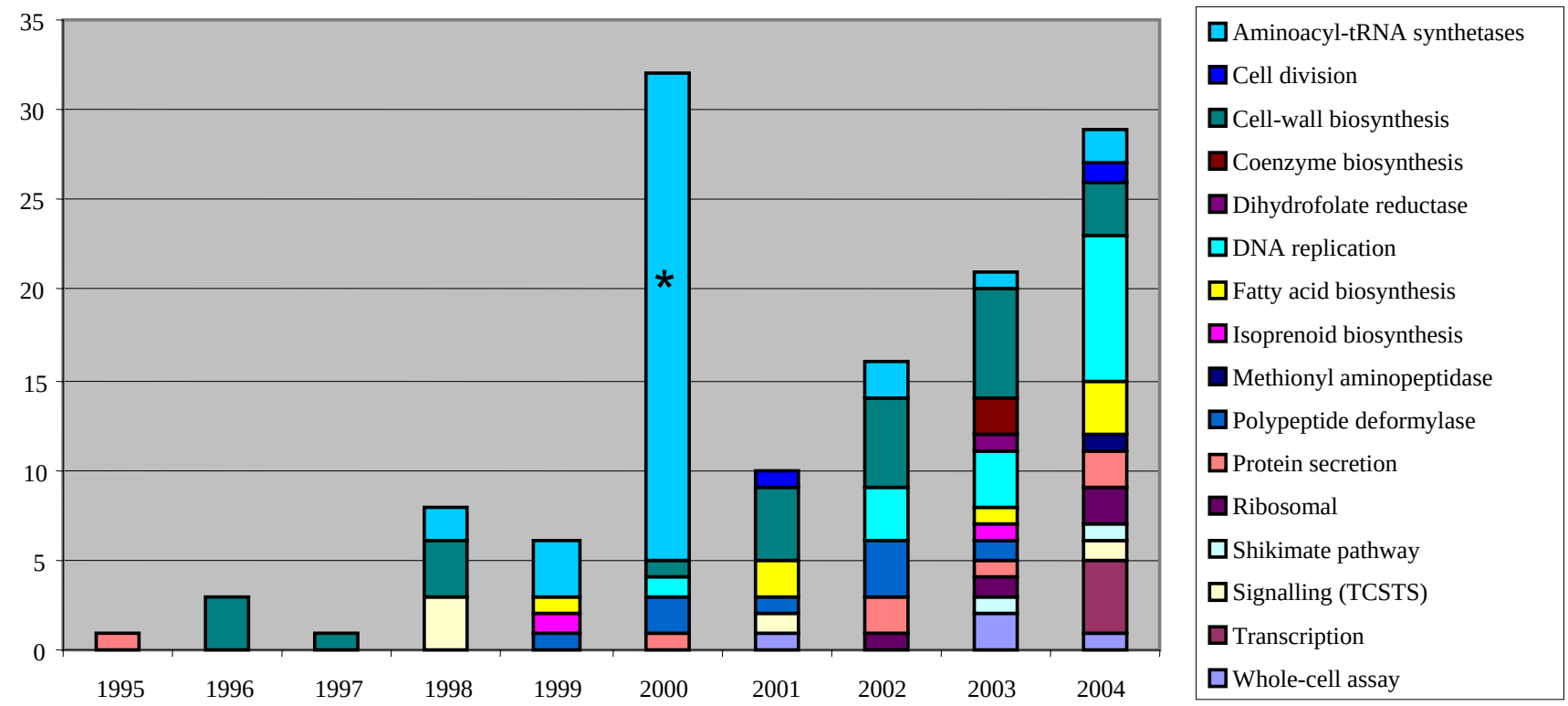
Antibacterial Leads Are Difficult to Find

Total targets/screens	**92**
Progressed to decision*	**77**
Terminated pre HTS	**7**
Completed HTS	**70**
Screens with tractable HITs	**18 (26% of HTS)**
# where HITs progressed to LEADS**	**5 (7% of HTS)**

**antibact activity & MOA; *progression/termination

Finding Antibacterial Leads Is Much Less Likely than for Other Therapeutic Areas

>100 HTSs on 60 Different Novel Targets !

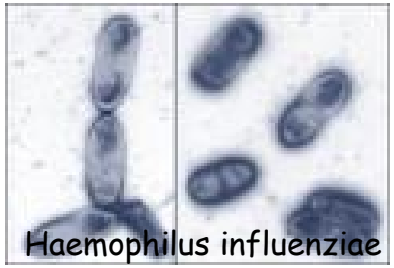


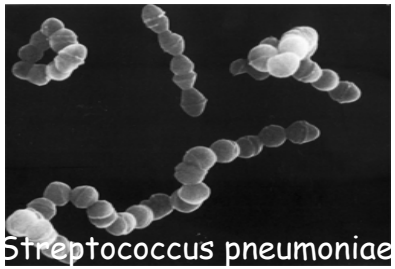
Published antibacterial screens by year and target class

“New” Targets Need Thorough Validation

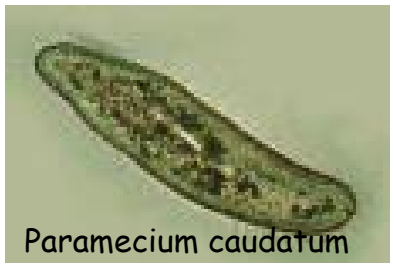
- MetRS
  - two different forms in Spn
- MurA
  - two copies, both need to be inhibited
- FabI
  - not present in Spn (FabK)

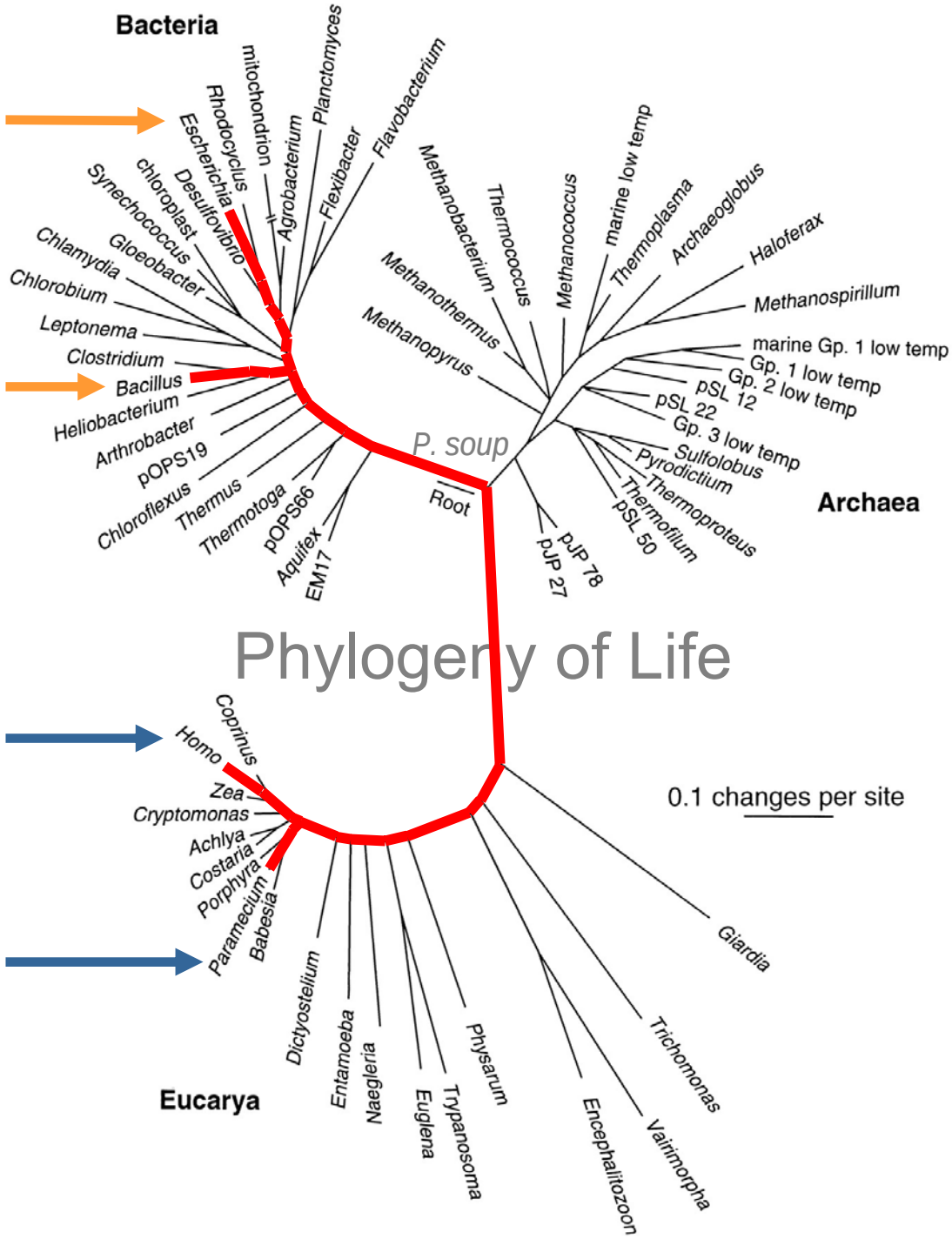
Them


Haemophilus influenziae

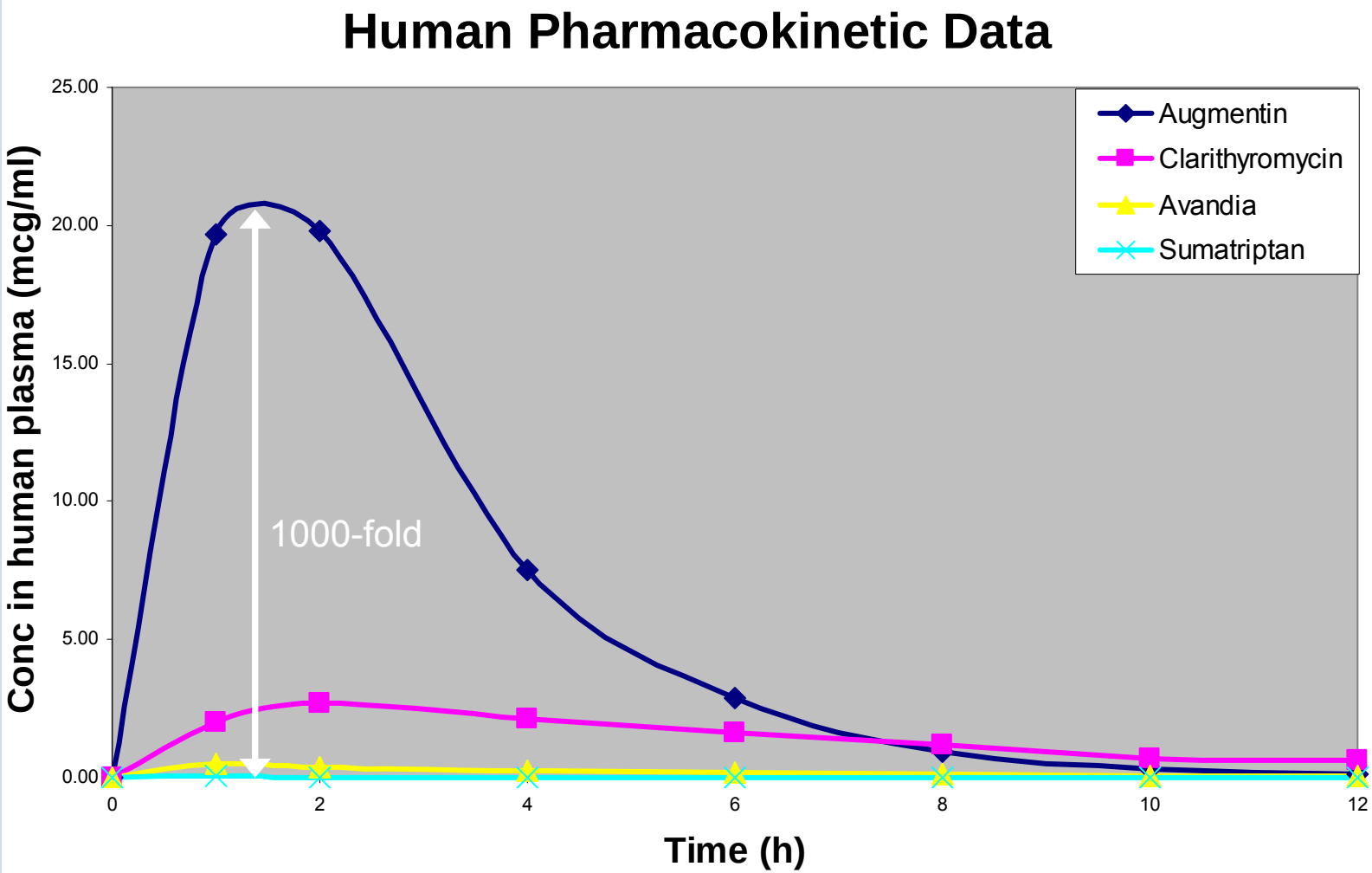

Streptococcus pneumoniae

Us


Paramecium caudatum


Bacteria
mitochondrion
Rhodocyclus
Escherichia
Planctomyces
Flavobacterium
Agrobacterium
Flexibacter
Desulfovibrio
chloroplast
Synechococcus
Gloeobacter
Chlamydia
Chlorobium
Leptonema
Clostridium
Bacillus
Heliobacterium
Arthrobacter
pOPS19
Chloroflexus
Thermus
Thermotoga
pOPS66
Aquifex
EM17
Root
P. soup
Methanobacterium
Thermococcus
Methanococcus
marine low temp
Thermoplasma
Archaeoglobus
Haloferax
Methanothermus
Methanopyrus
Methanospirillum
marine Gp. 1 low temp
Gp. 1 low temp
Gp. 2 low temp
pSL 12
pSL 22
Gp. 3 low temp
Sulfolobus
Pyrodictium
Thermoproteus
Thermofilum
pSL 50
pJP 78
pJP 27
Archaea
Phylogeny of Life
Coprinus
Homo
Zea
Cryptomonas
Achlya
Costaria
Porphyra
Paramecium
Babesia
Dictyostelium
Entamoeba
Naegleria
Euglena
Trypanosoma
Physarum
Giardia
Trichomonas
Vairimorpha
Encephalitozoon
Eucarya
0.1 changes per site

High [antibiotic] Required for Efficacy



R&D Resource Allocated by eNPV

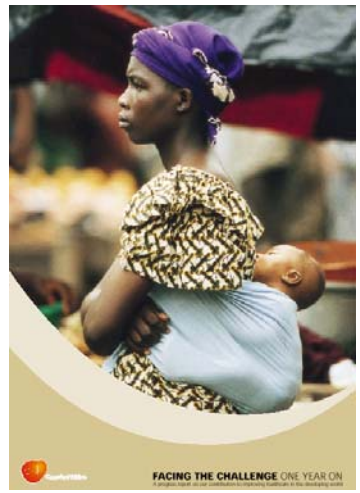
$$eNPV = \sum_{1}^{x} \left\{ \sum_{0}^{n} \frac{I_n}{(1 + r)^n} \right\}$$

- Value
  - Patient need
  - Financial value
- Developability (Probability of Success)
  - Scientific, medical, technical
  - Regulatory

Antibacterials Do Not Compete Well.

Infectious Disease Is Different

- Future ID medicines addressing medical need represent modest commercial opportunities
- We have responsibilities to our patients
  - Epidemics and bioterrorism
  - Diseases of the Developing World
    - TB and malaria discovery (Tres Cantos)
      - Global Alliance for TB Drug Development
      - Medicines for Malaria Venture



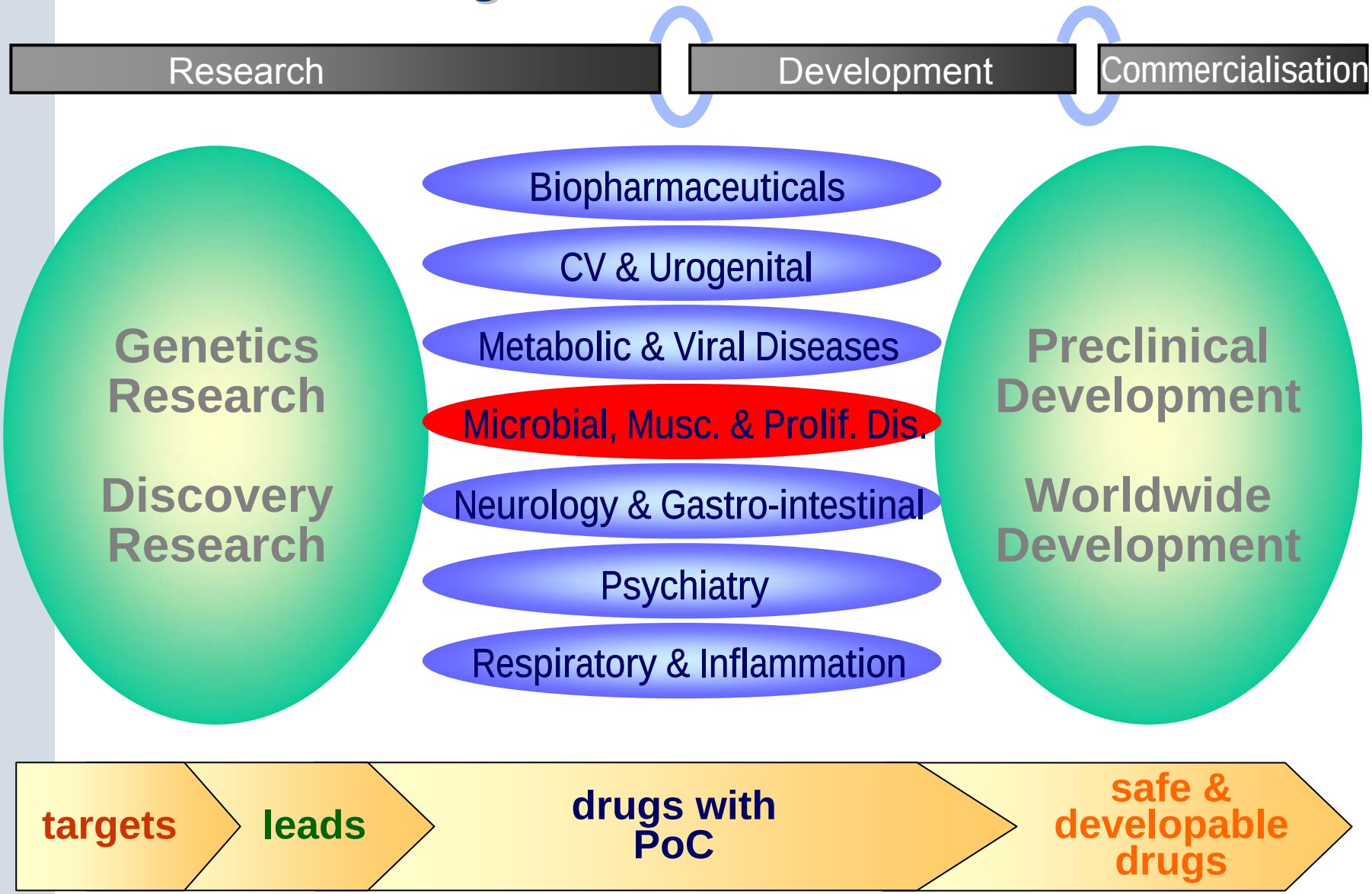
- Success against ID fuels a positive public perception

It's the Right Thing to Do.

Antibacterial Discovery: A New Strategy

- Organize R&D differently: CEDDs
- Focus only on community antibiotics
- Resource small number of clinically validated targets in a big way
  - Admit we cannot do everything
- Partner for sustainability
  - Little internal resource

GSK R&D Is “Big” and “Small”



Antibacterial Research at GSK

Collegeville, PA, USA

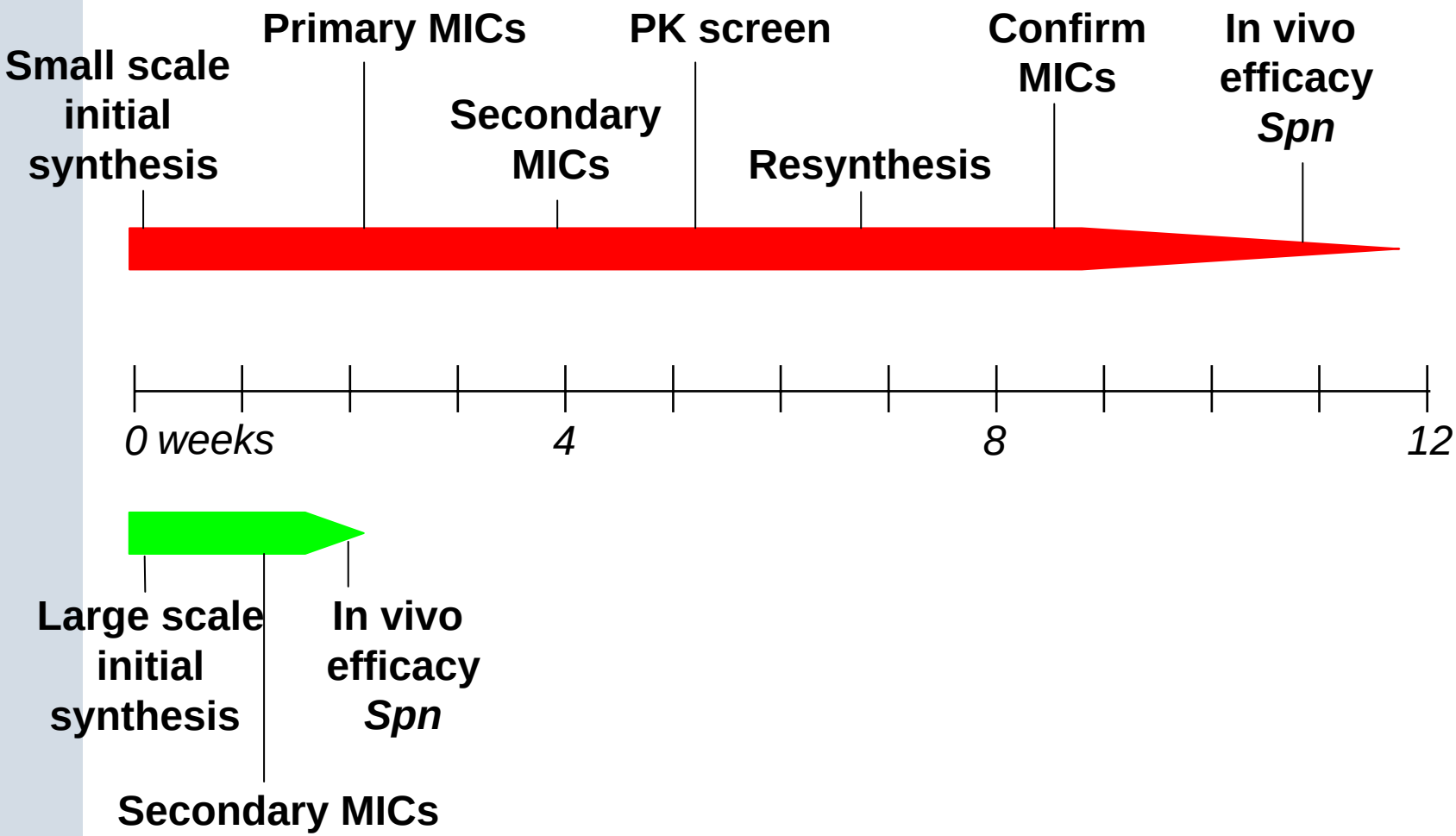
Tres Cantos, Spain

Harlow, UK

A Good Target Is Better than a New Target

- Need to cover atypicals eliminates some targets
  - cell wall, fatty acid biosynthesis, for example
- Triage leads on basis of developability
  - best leads inhibit protein or DNA synthesis
    - Don’t underestimate evolution!
- Throw the kitchen sink at it !
  - Big med chem teams can overcome obstacles
  - Microbiology focused entirely on progressing leads

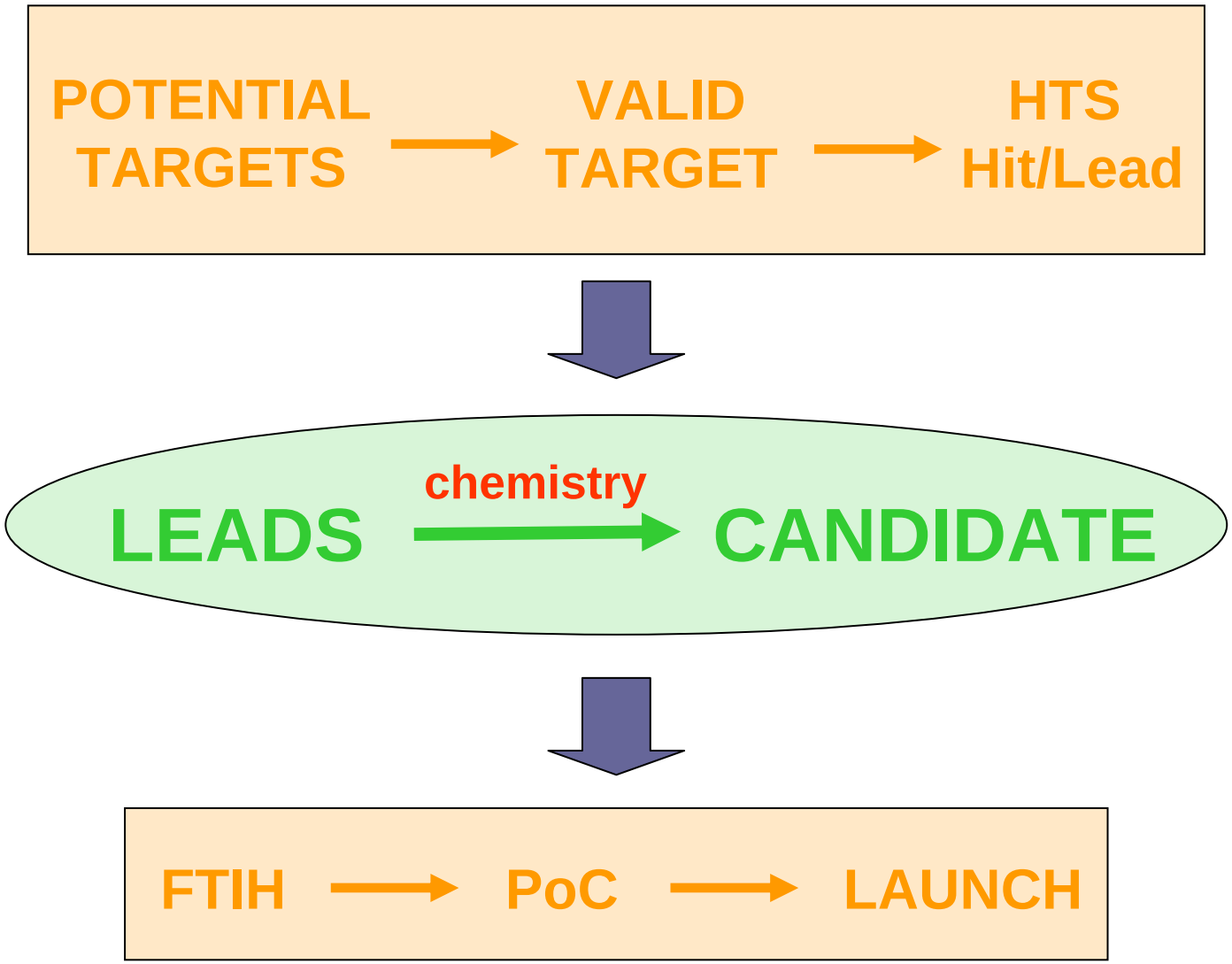
Test in Animals as Soon as Possible



Partnerships to Maintain Early Pipeline

- Groundwork laid (reagents, assays, hits, etc) for many additional targets
  - No internal resource to pursue
- GSK HTS screening technology and collection transformed
  - Re-screen antibacterial targets?
    - Many targets screened >5 years ago
- Partner with small/medium pharma to prosecute lead optimization on HTS hits

Typical Alliance Structure



Elements of Success

- Focus efforts on a single product profile
- Large med chem efforts on few targets
- Biology support now aimed only at advancing drug candidates
  - better validation, faster compound evaluations
- Corporate will (and resources) to succeed

Building the Right Molecule Is the Hard Part.